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Palladium Catalysis

Organotrifluoroborates and Monocoordinated Palladium Complexes as Catalysts—A Perfect Combination for Suzuki–Miyaura Coupling

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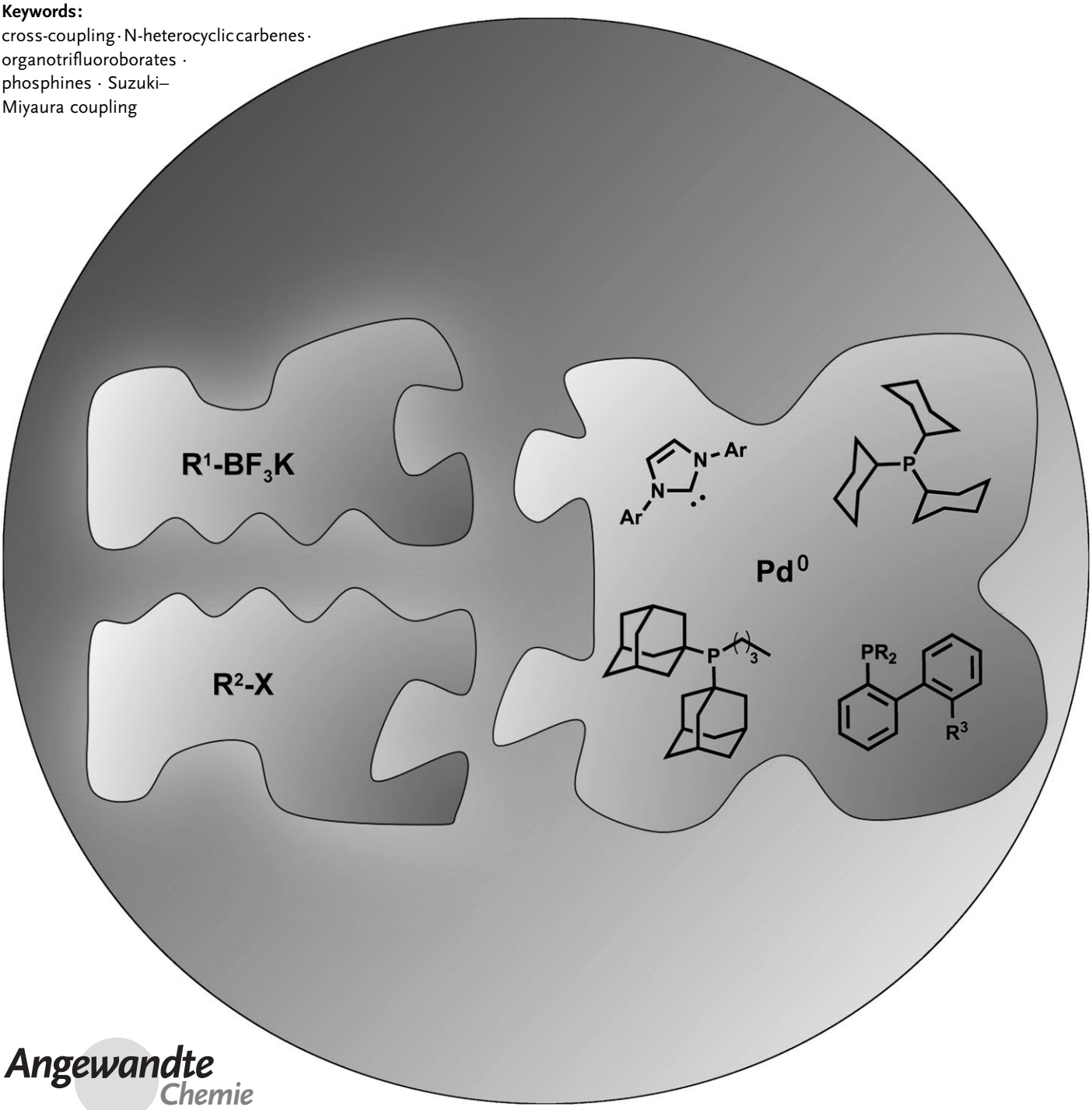

Monocoordinated palladium catalysts derived from sterically hindered, electron-rich phosphines or N-heterocyclic carbenes have revolutionized the Suzuki–Miyaura coupling reaction. The emergence of organotrifluoroborates has provided important new perspectives for the organoboron component of these reactions. In combination, these two components prove to be extraordinarily powerful partners for cross-coupling reactions.

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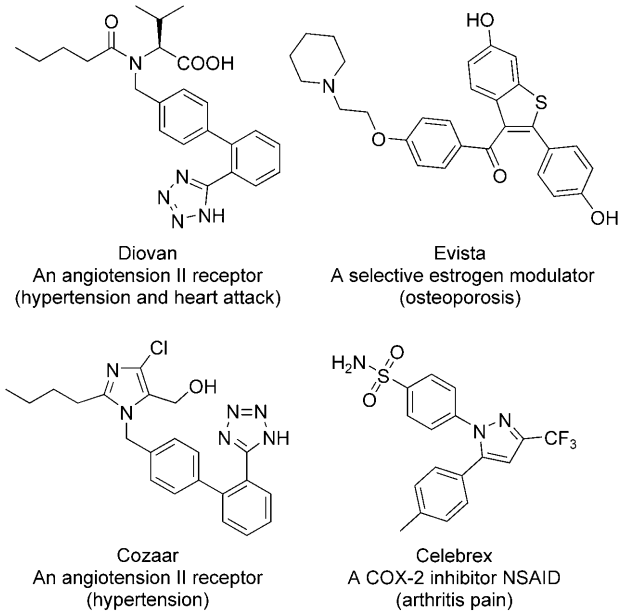
1. Introduction

Few reactions have influenced organic synthesis as greatly as the Suzuki–Miyaura reaction. First described in 1979,[1] this reaction has transformed the manner in which many target molecules are assembled. The reaction was initially developed to overcome the inadequacies of nucleophilic substitution reactions and in particular Ullmann coupling reactions for the creation of $C(sp^2)$–$C(sp^2)$ bonds. More recently, however, the true power of the method has been revealed by the vast number of catalyzed reactions between organoboron reagents and organic halides and pseudo halides.[2]

By revolutionizing fundamental strategies for key bond constructions in organic molecule synthesis, cross-coupling reactions have in turn transformed several chemical-based industries. Thus, the ability to create novel structures with ease by cross-coupling reactions has resulted in compounds emanating from pharmaceutical and agrochemical firms, as well as those generated in many materials-based companies that have changed dramatically over the years. As an example, many of the drugs in development in the pharmaceutical industry prior to the 1980s were based upon natural products and their analogues (for example, steroids, β-lactams, macrolactones, prostaglandins, and alkaloids). The establishment of cross-coupling protocols resulted in a substantial number of the top selling drugs in 2007 containing one or more biaryl systems (Scheme 1),[3] and many more possessing other structural features that could be installed by cross-coupling protocols. It is evident that cross-coupling reactions have become entrenched amongst the most powerful and important transformations in modern organic synthesis.[4]

As might be imagined for such an important process, thousands of studies in which the reaction has been employed have been published during the ensuing years, and an enormously broad range of reaction conditions have been described. Many of these studies have been devoted to important modifications and improvements on the original procedure. Among the latter contributions, the vast majority of these studies have focused on the expansion of the range of feasible organic electrophiles (aryl, heteroaryl, alkenyl, alkynyl, alkyl) and nucleofuges (iodides, bromides, phosphates[5]). Additionally, important studies concerning solvent effects (such as the influence of water[6] or ionic liquids[7]), the bases required, and other reaction parameters (for example, the application of sonication[8] or microwave irradiation[9]) have been conducted.



Scheme 1. Top selling pharmaceutical drugs in 2007 that contain biaryl linkages.

2. Ligand Development

Despite these enormous early efforts, rather significant gaps in the technology still remained. Some of the most pressing unresolved issues included: 1) The ability to use aryl chloride electrophiles,[10] which are much more readily available and less expensive than their bromide or iodide analogues, but inherently less reactive. Additionally, general

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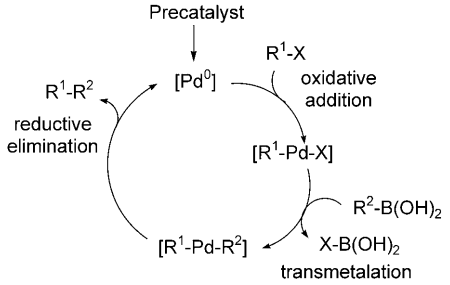
approaches were also lacking for the complementary sulfonates.[11] 2) Cross-coupling of sterically encumbered systems.[12] 3) Incorporation of alkyl halide and alkyl boron partners, which suffer from competitive β-hydride elimination reactions. 4) Effective cross-coupling of electron-deficient[13] and heteroaromatic organoboron reagents,[14] which are readily proto-deboronated under the same general conditions required for cross-coupling. Several research groups thus turned their attention toward these intransigent problems.

The solution for many of these challenges turned out to reside in the development of effective palladium/ligand catalyst systems. Thus, one of the more important recent advances to evolve from these studies has been the introduction of sterically bulky, electron-rich ligands as partners for the metal precatalysts.[10,15] The advent of these ligands has virtually eliminated many of the limitations of the original Suzuki–Miyaura coupling reaction outlined above. Furthermore, the use of these ligands has allowed the reaction to be performed at room temperature[16] with much lower catalyst loadings.

Careful consideration of the mechanistic aspects of the catalytic cycle (precatalyst activation, oxidative addition, transmetalation, and reductive elimination, Scheme 2) has



Scheme 2. General catalytic cycle for the Suzuki–Miyaura cross-coupling reaction.

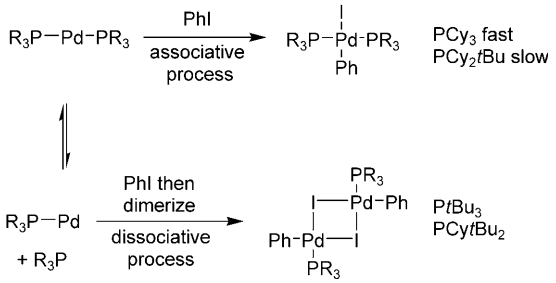
provided insight into features required in the catalyst systems to achieve more satisfactory results.

Although not often appreciated, an understanding of the nature and activation of the precatalyst (for example, $Pd(OAc)_2$ versus $[Pd_2(dba)_3]$) has proven incredibly useful in clarifying key observations and trends in cross-coupling reactions, and also in improving overall catalyst performance.[17] For example, dba has been determined to play a tremendously active role as a ligand in palladium-catalyzed cross-coupling reactions, by controlling the rates of the oxidative addition as well as the concentration of key monocoordinated palladium species in solution. Whether one uses $[Pd_2dba_3]$ or $Pd(OAc)_2$ as a precatalyst can thus have a profound effect on the success of any given transformation.

Major efforts have been invested in improving the oxidative addition step, which can be the rate-determining step, of cross-coupling reactions. One of the keys to finding improved catalyst systems was the realization that sterically encumbered ligands led to highly reactive, monocoordinated, 12-electron organopalladium complexes. As a result of their extreme electron deficiency and their diminished steric shielding, these $[LPd^0]$ species facilitated the oxidative addition step. In a series of reports concerning oxidative addition, Hartwig and co-workers revealed that a monophosphine complex is the most likely Pd^0 intermediate participating in the catalytic cycle when palladium catalysts bearing sterically encumbered phosphine ligands, such as $(o\text{Tol})_3P$, are used.[18] Similar results were subsequently found with other hindered ligands, including $P(t\text{Bu})_3$ and QPhos.[19]

Brown and co-workers followed with a detailed study that demonstrated the sensitivity of the oxidative addition of $[Pd(PR_3)_2]$ complexes to the steric effects of the alkyl groups on the phosphine.[20] The more sterically encumbered complexes (for example, $[Pd(Pt\text{Bu}_3)_2]$) undergo oxidative addition with aryl halides by a dissociative mechanism, whereas the oxidative addition in less sterically encumbered intermediates proceeds by an associative process (Scheme 3).

Hartwig has summarized the effect of ligand bulk on the oxidative addition process by noting that the presence of sterically bulky ligands in the palladium(0) complex will



Scheme 3. Steric effects determine whether an associative or dissociative oxidative addition mechanism is followed.

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increase the energy of the ground state in such [L_2Pd^0] complexes more than that of the low-coordinate, dissociated intermediate [LPd^0] (Figure 1).[15a] Consequently, the use of

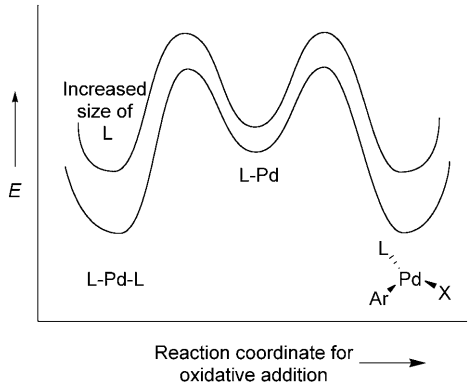
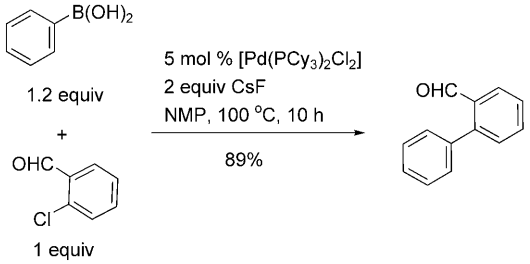


Figure 1. Steric effects in palladium(0) complexes as shown by an energy versus reaction coordinate diagram.

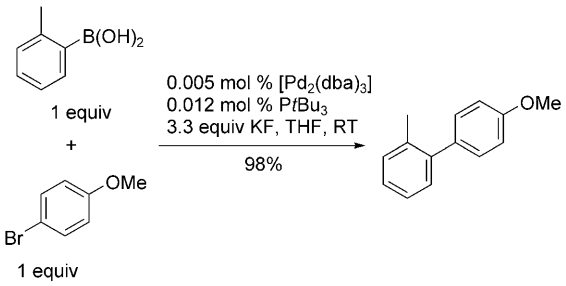
more highly hindered ligands provides a smaller energy difference between the ground state and the reactive [LPd^0] intermediate, thereby facilitating the oxidative addition process.

Electronic effects also play a role in facilitating oxidative additions. Thus, the generation of a monocoordinated Pd^0 complex is perhaps a necessary, but not sufficient, criterion for achieving facile reactions with recalcitrant halides. Electron-rich ligands on the metal center further lower the energy of activation for the oxidative addition step of the process. This enables more facile insertion of the metal center into the carbon–chlorine bonds of aryl chlorides, for example, as well as reaction with the carbon–halogen bonds in alkyl halides, which are much more reluctant to undergo oxidative addition than the corresponding aryl halides.[2a] As a consequence, lower reaction temperatures can generally be employed. Shen appears to be the first to have recognized the advantages of utilizing sterically bulky, electron-rich phosphines in Suzuki–Miyaura reactions.[21] He employed tricyclohexylphosphine (PCy_3) as a ligand for the cross-coupling of electron-deficient aryl chlorides with aryl boronic acids [Eq. (1)].



(1)

Shortly thereafter, Fu independently demonstrated that such electron-rich, sterically encumbered phosphines could be utilized to address a number of unresolved issues within the realm of Suzuki–Miyaura cross-coupling reactions.[2d] For example, aryl bromide, iodide, and triflate electrophiles could all be cross-coupled under extremely mild conditions with boronic acids by utilizing either PCy_3 or $P(t\text{Bu})_3$ ligands [Eqs. (2) and (3)]. Most impressively, unactivated aryl chlorides were demonstrated to be effectively coupled in high yields [Eq. (4)].



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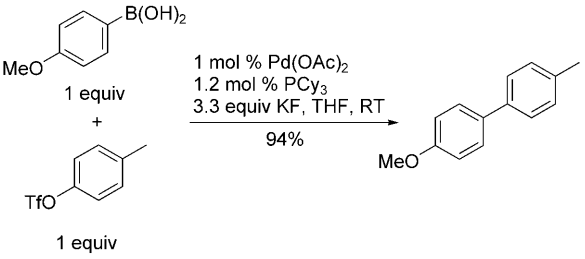

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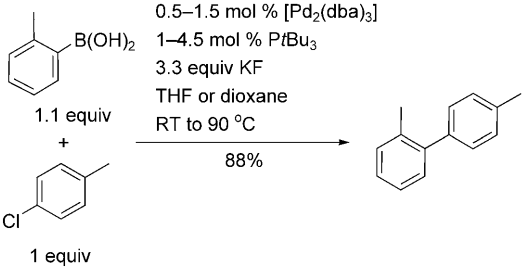
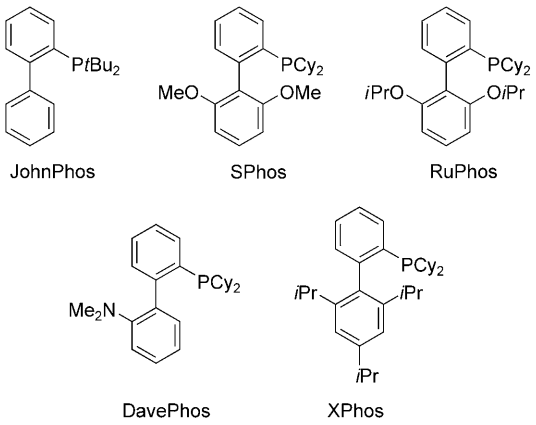


(4)

Perhaps the most effective and broadly useful ligands introduced to date are the family of dialkylbiaryl phosphine ligands developed by Buchwald and co-workers (Scheme 4).[15c] These ligands, which exhibit impressive air stability, possess variable design elements that have made them nearly ideal within a number of cross-coupling settings. Their sterically imposing, electron-rich nature is thought to favor the monocoordinated [LPd^0] form of the catalyst, thus making them highly reactive in the oxidative addition step of the catalytic cycle.

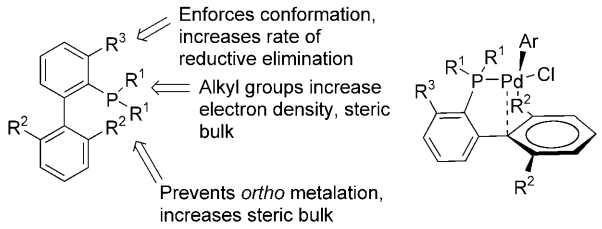
There are other benefits to using such monocoordinated complexes, including faster transmetalation (which could reduce the amount of competitive proto-deboronation in Suzuki cross-coupling reactions), and more rapid reductive elimination compared to [L_2Pd^0] species.[22] The second point is particularly important in cross-coupling reactions involving alkyl groups, wherein a competition arises between reductive elimination and β-hydride elimination. Reductive elimination involves a decrease in the coordination number about the metal center, and thus highly hindered ligands should



Scheme 4. The dialkylbiaryl phosphine ligands developed by Buchwald and co-workers.

facilitate the process. In β-hydride elimination, the coordination number either remains the same or is increased, and consequently sterically encumbered ligands are expected to inhibit this process. The overall effect of using sterically imposing, electron-rich ligands is to minimize the competing β-hydride elimination or other side reactions that could interfere with the collapse of the diorganopalladium intermediate that closes the catalytic cycle.[19b]

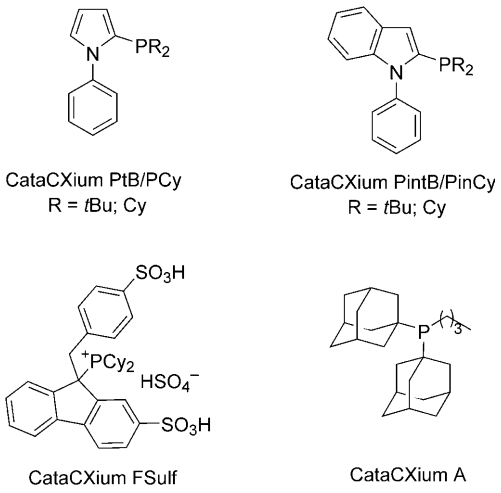
Other significant features of the ligands designed by the Buchwald research group include the non-phosphine-bearing aryl ring of the biaryl unit, which stabilizes the Pd^0 catalyst through favorable interactions with the π system, and the installation of substituents at the *ortho* position of this ring, which prevent *ortho* metalation and also provide a further increase in steric bulk (Scheme 5).[15c,23]



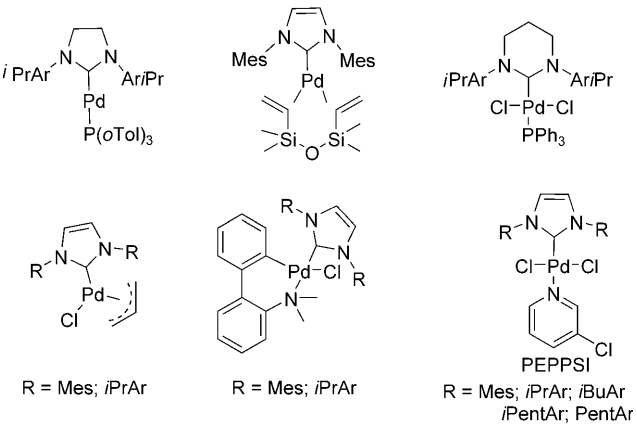
Scheme 5. Structural features of dialkyl biaryl phosphine ligands and stabilization by the non-phosphine-bearing aryl ring.

Other highly successful ligand systems that take advantage of similar design elements have been reported. Perhaps most prominent among these is the CataCXium family of ligands (Scheme 6).[24]

Finally, N-heterocyclic carbene (NHC) systems have also proven extraordinarily successful for many of the same reasons as those detailed for the phosphine systems (Scheme 7). NHCs are electron-rich, σ-donor ligands with a negligible capability to accept π back donation from the metal center. This feature, combined with their inherent instability in the free state, minimizes their dissociation from the metal center, thereby increasing the stability of the catalyst. Contributions from the research groups of Herrmann,[25]



Scheme 6. CataCXium ligands.



Scheme 7. Monocoordinated palladium NHC complexes used in palladium catalyzed cross-coupling. *i*PrAr = 2,6-diisopropylphenyl.

Beller,[26] Nolan,[27] Glorius,[28] and Cloke[29] have been influential in this area, and of particular note is the introduction of the PEPPSI family of NHC catalysts by Organ et al.[15b,e] As with the phosphine ligands, highly sterically encumbered systems work the best, and the ligand/palladium ratio can play a large role in the activity of the catalyst.

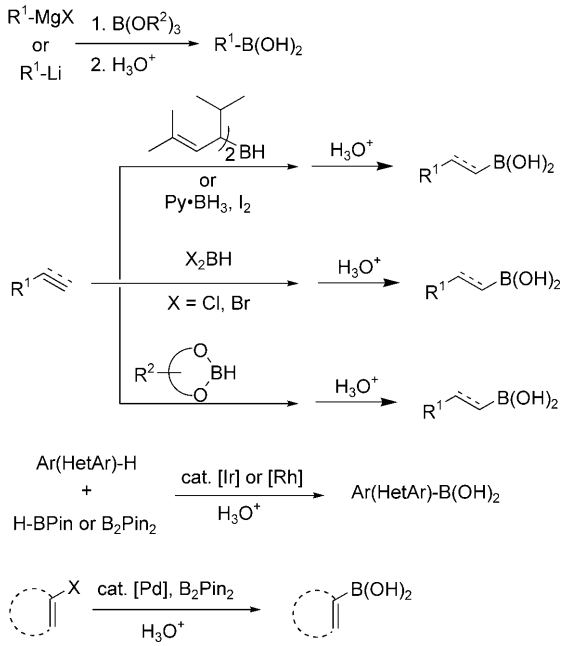
3. Comparison of Various Organoboron Species

Tremendous effort has been exerted to generalize and perfect the Suzuki–Miyaura reaction. For over 30 years, these labors revolved largely around enhancing the various reaction conditions, and most recently the metal–ligand complex. Curiously, one of the most important components of the reaction, the organoboron partner, has undergone little serious development.

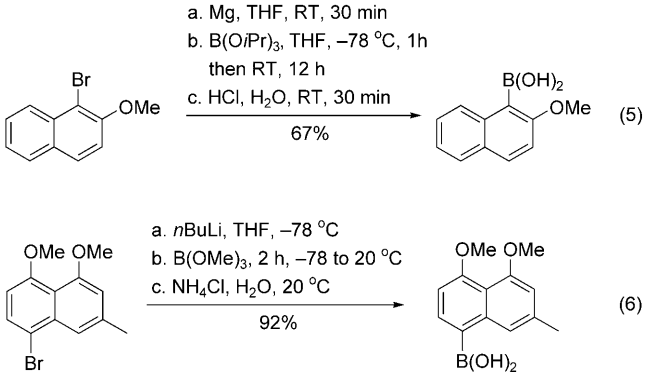
In assessing the value of the available organoboron nucleophiles for cross-coupling, direct comparisons must be viewed with some caution. Some research groups optimize reaction conditions for one class of organoboron species (for

example, boronic acids), and then compare other reactive partners (boronate esters or borates) under the same experimental conditions.[30] This practice leads to false conclusions, because the experimental protocol for one set of organoboron partners are very often completely different from those required for another. The most reliable assessment of the relative efficacy of organoboron reagents in cross-coupling reactions is best made under circumstances where each class of organoboron reagent has been optimized separately.

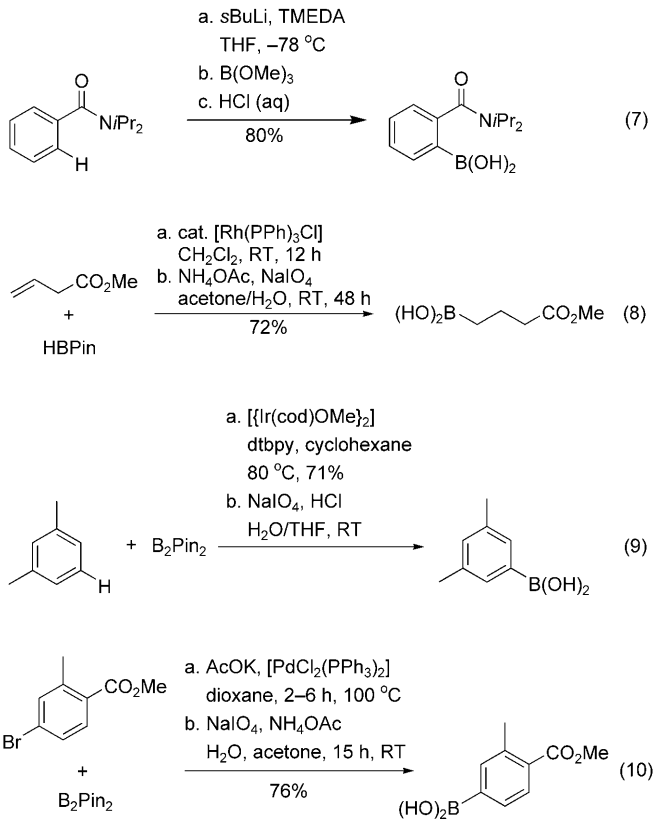
For many logical reasons, boronic acids have become the boron reagents by which all others are measured for their suitability in Suzuki–Miyaura cross-coupling reactions. They are readily prepared by an increasing number of routes [Scheme 8, Eqs. (5)–(10)],[31] and thousands of structurally



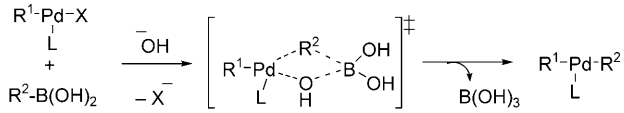
Scheme 8. General routes to prepare boronic acids.



diverse reagents are now commercially available. Although there are notable exceptions (for example, cyclopropylboronic acid, vinylboronic acid,[32] and many heteroarylboronic

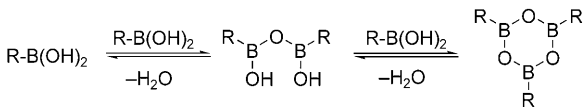


acids[14,32,33]), boronic acids are reasonably stable upon storage. They are mechanistically primed for cross-coupling because the hydroxy groups on the boron atom coordinate with the generated organopalladium halide intermediate, thereby facilitating what would otherwise be a very difficult transmetalation from a weakly nucleophilic boron center (Scheme 9).[34]



Scheme 9. Substituent effects on transmetalation of organoboron reagents. X = halogen, L = phosphine.

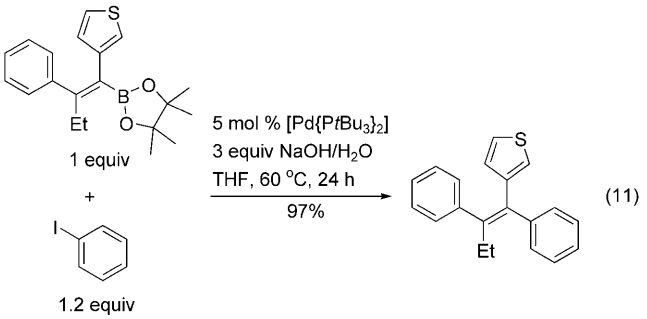
Despite their widespread use, boronic acids have several distinct drawbacks and limitations. First, the boronic acids are not monomeric species, but rather exist as dimeric and cyclic trimeric anhydrides (Scheme 10).[35] This has a minimal effect on their ability to cross-couple, because these anhydrides are



Scheme 10. Boronic acids are in equilibrium with their dimeric and trimeric anhydrides.

readily hydrolyzed back to the boronic acids under the aqueous conditions often used for cross-coupling reactions. However, the mixture of species present does occasionally lead to difficulties in purification, with the boronic acids often appearing as waxy solids instead of crystalline solids or free-flowing powders. As a consequence of their relatively facile proto-deboronation, even under the most highly optimized conditions, a substantial (20–50%) excess of the boronic acids is used in most typical cross-coupling reactions. Finally, boronic acids are sensitive to reagents commonly used in the course of routine organic synthesis, and thus they are rarely carried through a synthetic sequence in which the organic substructure is modified. Consequently, boronic acids are either purchased or prepared and immediately cross-coupled with no further elaboration or increase in molecular complexity. This is inherently restrictive and severely limits strategic planning in complex molecule or diversity-oriented library synthesis.

Boronate esters such as pinacol boronates might be thought of as protected forms of boronic acids which allow a limited number of transformations to be carried out on the organic substructure in the presence of the boron moiety.[36] Boronate esters are monomeric species, and the pinacol boronates, in particular, facilitate purification because many are crystalline solids. Some boronate esters can be purified by chromatography, although they often suffer partial hydrolysis in the process. Perhaps the biggest drawbacks in using boronate esters as surrogates for boronic acids is the loss of atom economy in the process and the fact that the most common and most stable derivatives, the pinacol boronates, are derived from an alcohol that is reasonably expensive. Cross-coupling reactions of pinacol boronates can often be effective when carried out under optimized conditions [Eqs. (11)–(13)].[37]



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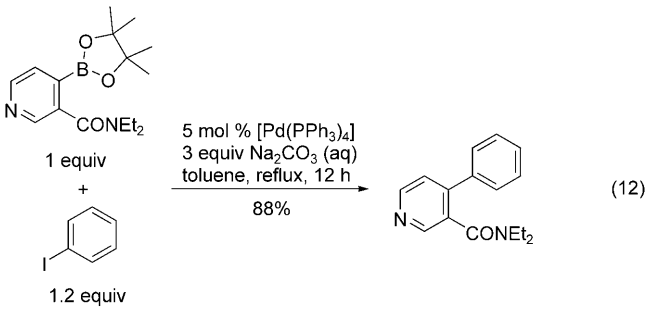

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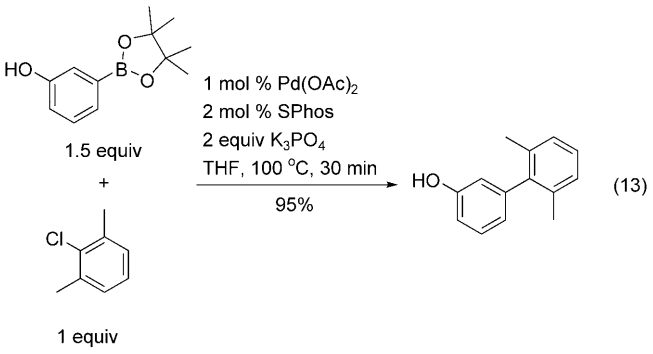

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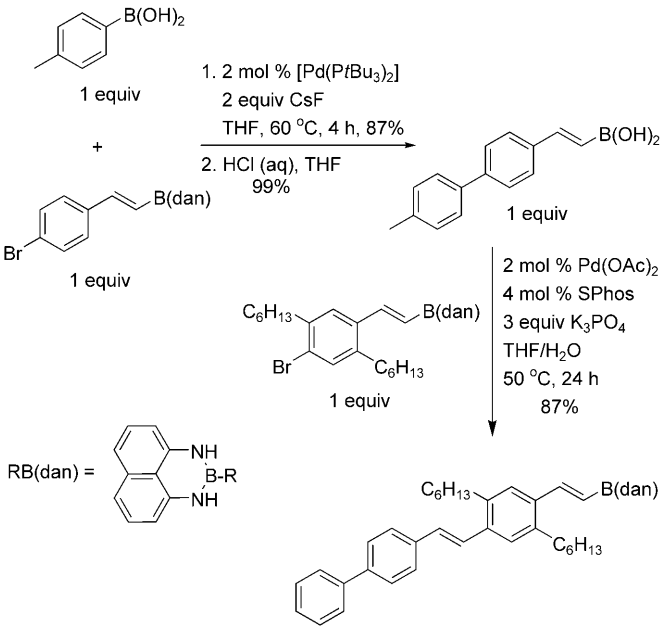
Other alternatives to pinacol boronates have recently been promoted as protected forms of boronic acids that allow more effective protection of the boronic acid group. For example, Suginome and co-workers have developed 1,8-naphthalenediaminatoboranes RB(dan) as a means to cross-couple a boronic acid in the presence of a second (protected) boron species (Scheme 11).[38] Although the "dan" groups do

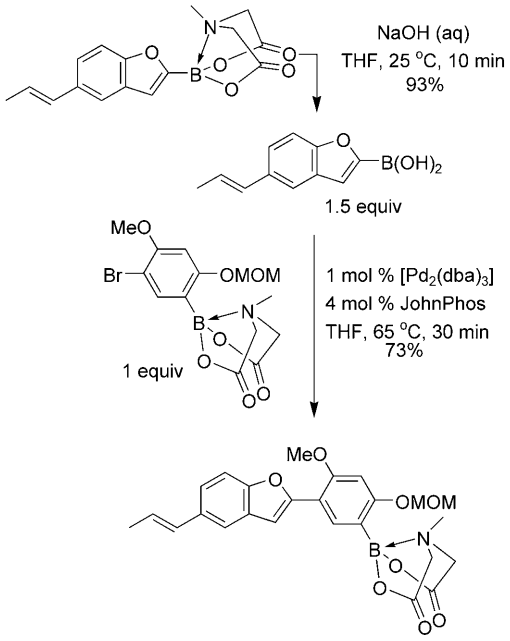


Scheme 11. Cross-coupling of Suginome's "dan" complexes.

provide effective protection of the boronic acid function, the drawback to this protection scheme is that the "dan" boronates cannot be cross-coupled directly, but must first be hydrolyzed back to the boronic acids. This not only decreases the synthetic efficiency of the process, but also exposes the cross-coupling step to the same limitations inherent in all boronic acid coupling reactions.

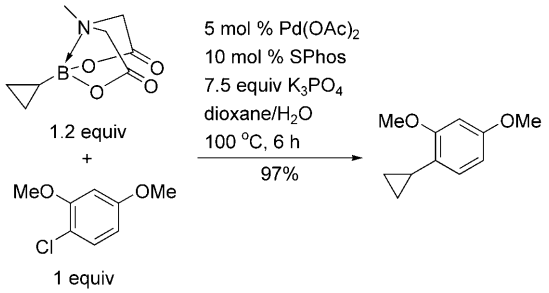
In a similar manner, the *N*-methyliminodiacetic acid (MIDA) boronates of Gillis and Burke have been developed as bench-stable, crystalline materials that possess a number of desirable features.[32b,39] For example, they can be readily purified by chromatography, and the MIDA moiety serves as a highly effective protecting group for the boron center. Consequently, a wide range of useful reactions can be carried

out on functionalized MIDA boronates, thus allowing an unprecedented increase in the molecular complexity of the organic substructure of the organoboron species. The Achilles heel of the MIDA boronates again lies in their cross-coupling capabilities, which more or less mimic those of boronic acids. Thus, in several protocols the MIDA boronates are actually hydrolyzed back to the boronic acid prior to coupling (Scheme 12), which severely reduces the synthetic efficiency.



Scheme 12. Cross-coupling of Burke's MIDA complexes.

Furthermore, as is the case of the "dan" reagents, the MIDA reagents have the same critical flaws in coupling as boronic acids. For example, the coupling of MIDA reagents susceptible to proto-deboronation (in particular, cyclopropyl and heteroaryl systems) requires a significant (20–50%) excess of the reagents [Eq. (14)]. These factors, combined with the loss of atom economy and the use of an extremely expensive protecting group, render the MIDA boronates less than ideal.



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4. Organotrifluoroborates and Monocoordinated Palladium Catalysts: "Hitting the Sweet Spot"

Although organotrifluoroborates (RBF_3K) had been known for some time,[40] it was not until Vedejs et al. reported their preparation with KHF_2 that these reagents became widely available [Eq. (15)].[41] Virtually any organoboron compound with two labile substituents can be rapidly and

(15)

Y = halide, OR, NR_2, allyl

efficiently converted into the corresponding potassium organotrifluoroborate by using this procedure. The reaction occurs within minutes to two hours depending on the nature of the starting material. Well over 400 structurally diverse RBF_3K compounds have been reported to date, and virtually every one of these salts has been a crystalline solid or free-flowing powder; thus, isolation of the organotrifluoroborates is normally quite simple. All of the solvents from the reaction with KHF_2 are removed in vacuo, and hot acetone or acetonitrile is then added. The organotrifluoroborates are soluble in these solvents, whereas the KF by-product is not. Filtration thus removes the KF, and cooling the solution often leads to direct crystallization or precipitation of the desired RBF_3K. Solvents such as Et_2O or hexane can be added in recalcitrant cases to precipitate the organotrifluoroborate. Another isolation method that works extremely effectively is continuous extraction: A simple Soxhlet extraction apparatus can be utilized to isolate the organotrifluoroborate. After removal of the solvent as above, the RBF_3K/KF solids are placed in the thimble of the extractor, and hot acetone or acetonitrile is used to dissolve the organotrifluoroborate, leaving the KF in the thimble. More than 100 g of material can be processed quite easily with this simple and effective method.

In addition to the advantages of stability, favorable physical properties, scalability, and operational simplicity that are inherent to the organotrifluoroborates, both atom economy and price speak clearly in favor of their use (Table 1).[42] With the exception of the boronic acids themselves, the organotrifluoroborates are by far the most economical and atom-efficient reagents available.

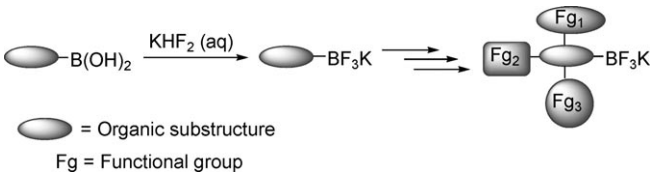
Table 1: Relative economies of boron substituents.

	Price in $ per mole equiv	Mass in derivatives
KHF_2	5.80[a]	96.09
pinacol	57.31[a]	116.16
1,8-naphthalenediamine (dan)	51.41[b]	156.18
N-methyliminodiacetic acid (MIDA)	697.40[a]	145.11

[a] Aldrich. [b] TCI America

Unlike boronic acids, the organotrifluoroborates are incredibly robust materials, capable of withstanding a number of reaction conditions that might be utilized to elaborate the organic substructure, thus allowing the molec-

ular complexity to be increased while keeping the carbon–boron bond intact for further transformation (Scheme 13).[42c] Transformations examined to date include a variety of



Scheme 13. Increasing the molecular complexity in organotrifluoroborates.

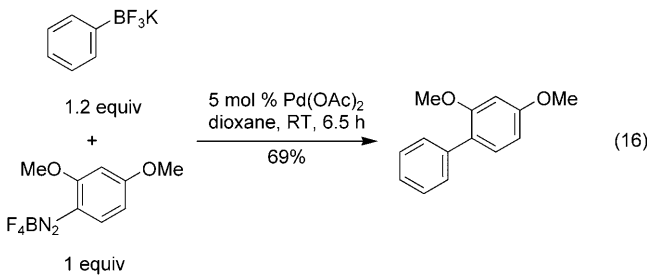
oxidations,[43] Wittig and related alkenation reactions,[44] reductive aminations,[45] substitution reactions,[46] metal–halogen exchange reactions,[47] condensation reactions,[48] 1,3-dipolar cycloadditions,[49] and cross-coupling reactions.[50]

Of greatest significance, perhaps, is the value of using organotrifluoroborates in cross-coupling reactions. Virtually all classes of organotrifluoroborates (aryl, heteroaryl, alkenyl, alkynyl, and alkyl) have demonstrated the ability to undergo cross-coupling reactions. In these transformations, the organotrifluoroborates display demonstrably high resistance to the competitive proto-deboronation reaction that appears to affect all other organoboron reagents. Consequently, the organotrifluoroborate can be used in nearly all cases in near stoichiometric amounts relative to the electrophilic cross-coupling partner, thereby increasing the efficiency and lowering the cost.

In many cases, and for a variety of reasons, organotrifluoroborates are demonstrably superior to other organoboron reagents not only in terms of versatility and their favorable chemical and physical properties, but also because of their cross-coupling capabilities. As outlined below, the combined use of organotrifluoroborates and monocoordinated palladium complexes as catalysts makes them a formidable combination for the construction of organic molecules by cross-coupling reactions.

4.1. Cross-Coupling with Aryl and Heteroaryl Trifluoroborates

Genêt and co-workers were the first to recognize the value of organotrifluoroborates in coupling reactions, whereby they investigated their use in conjunction with aryl diazonium salts [Eq. (16)].[51] Many aryl bromides were subsequently found to be viable substrates with organotrifluoroborates; the reactions were successful with relatively low catalyst loadings in the absence of additional ligands in MeOH [Eq. (17)]. In some cases water could be used as the solvent, and often these reactions were completely insensitive to oxygen.[52]



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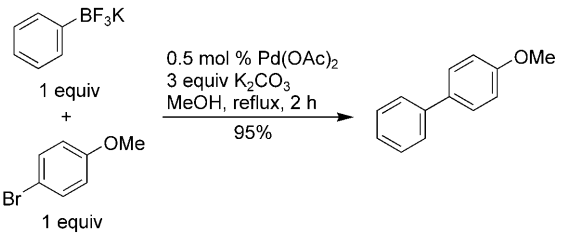
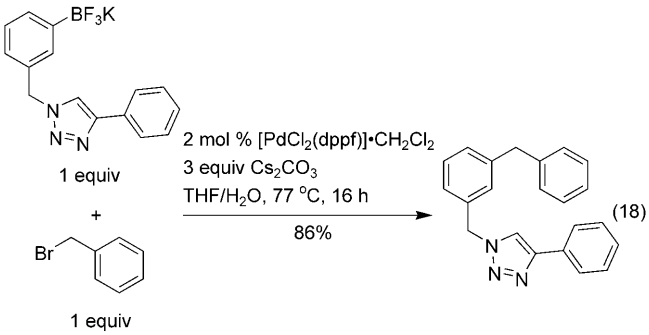


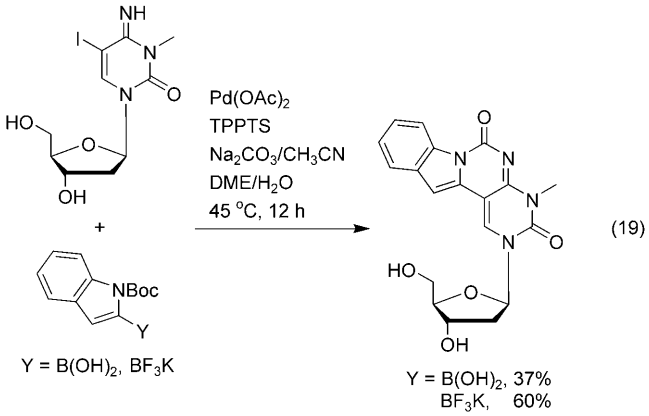
(17)

There are cases where aryl trifluoroborates have proven vastly superior to boronic acids and pinacolboronates in the absence of additional optimized ligands. For example, aryl trifluoroborates can be coupled with equimolar amounts of benzylic bromides to give high yields of the desired products [Eq. (18)];[53] previously reported procedures with boronic acids employed 1.5–2.0 equivalents of the organoboron reagent to avoid homocoupling of the halide.[54]



(18)

There are particular advantages in utilizing organotrifluoroborates for heteroaryl cross-coupling reactions. For example, in the course of synthesizing fluorescent nucleosides, Sekine and co-workers attempted to cross-couple an indoloboronic acid with a heteroaryl iodide.[55] The yield in this transformation was only 37% [Eq. (19)]. Simply switch-



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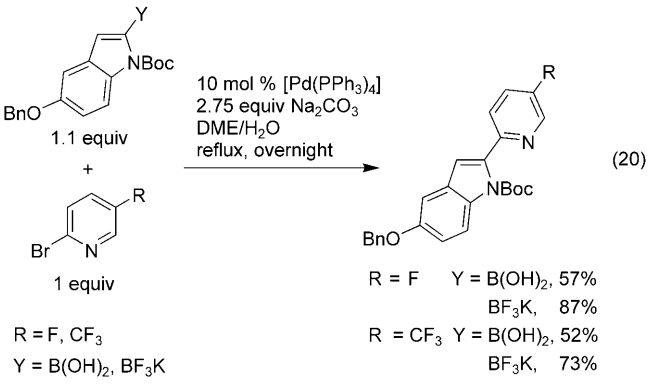
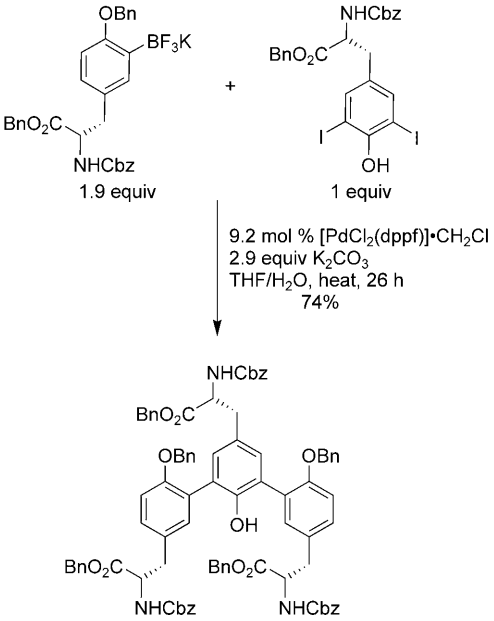
ing to the corresponding organotrifluoroborate resulted in the yield being improved to 60%. Similar differences were observed by Meggers and co-workers in their synthetic approach to protein kinase inhibitors [Eq. (20)].[56] In this



(20)

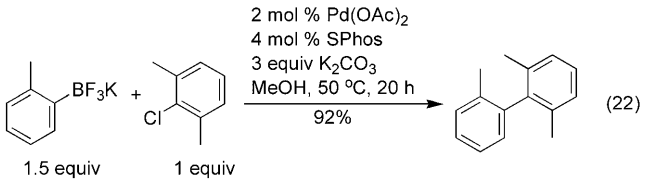
study, the superiority of the organotrifluoroborates for cross-coupling was attributed to suppression of the indole homocoupling that occurred when the analogous boronic acids were utilized.

An even more spectacular example is demonstrated by the synthesis of trityrosine through a double biaryl coupling. The transformation involving the aryl trifluoroborate occurs in 74% overall yield, whereas the corresponding pinacol boronate yielded none of the desired product [Eq. (21)].[57]



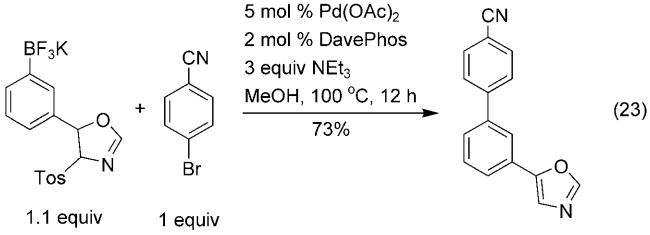
(21)

However, as the steric and electronic demands on the system are increased, the need for more highly effective ligands becomes evident. Barder and Buchwald were the first to apply monoligating ligands with enhanced properties to the cross-coupling of aryl trifluoroborates.[58] This seminal report detailed the use of aryl trifluoroborates with a variety of aryl chloride electrophiles, including challenging electron-rich, sterically encumbered substrates [Eq. (22)]). The method is competitive with the very best methods developed for the cross-coupling of traditionally challenging aryl chlorides with boronic acids.[59]



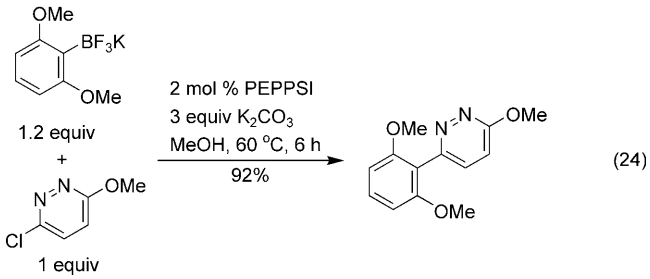
(22)

An adaptation of this method was utilized to convert sulfonyloxazoline-substituted aryl trifluoroborates into oxazolinyl biaryls through a one-pot process in which the cross-coupling occurs together with sulfinate elimination.[48] Among the variety of monoligating ligands examined, DavePhos proved to be the most efficacious for this process [Eq. (23)].



(23)

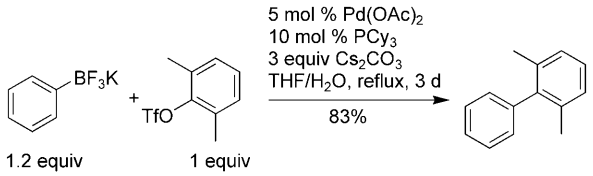
The PEPPSI catalysts developed by Organ et al. have also been used to advantage in the cross-coupling of aryl trifluoroborates with both aryl and heteroaryl chlorides under conditions that are again comparable to those of the corresponding boronic acids [Eq. (24)].[60]



(24)

Aryl and heteroaryl triflates are highly valued substrates for cross-coupling because of their ready availability from phenols. Although electron-poor aryl triflates undergo coupling without the need for additional ligands under the conditions designed for aryl bromides (0.5 mol% $Pd(OAc)_2$, K_2CO_3, MeOH),[61] electron-rich triflates provided only trace amounts of product, and the use of $[PdCl_2(dppf)]$ as a precatalyst was also ineffective.[62] However, high yields of the desired products could be realized by using a monoligating

ligand (PCy_3) in conjunction with the aryl and heteroaryl trifluoroborates [Eqs. (25) and (26)], once again reinforcing the synergistic benefits of these two partners.



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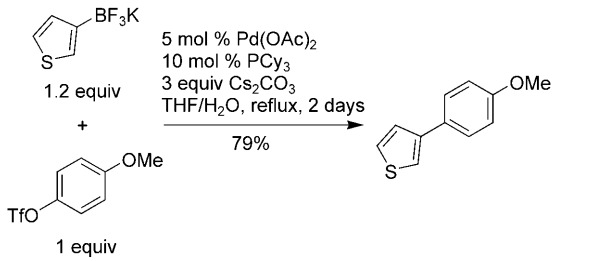
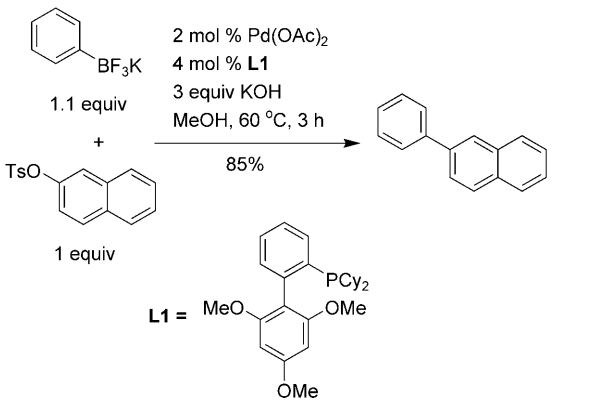


(26)

Aryl mesylates and tosylates are notoriously difficult substrates to coerce to undergo cross-coupling reactions,[63] but their hydrolytic stability and low cost compared to triflates provide distinct advantages as cross-coupling partners. Wu and co-workers reported reaction conditions [Eqs. (27) and (28)][64] for aryl trifluoroborates that were generally milder and required much less boron reagent than reported for the corresponding boronic acids [Eq. (29)]).[63] A novel indolylphosphine ligand has also been employed to allow the coupling of a single aryl tosylate with an organo-



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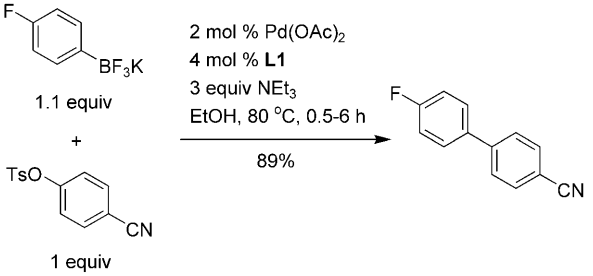

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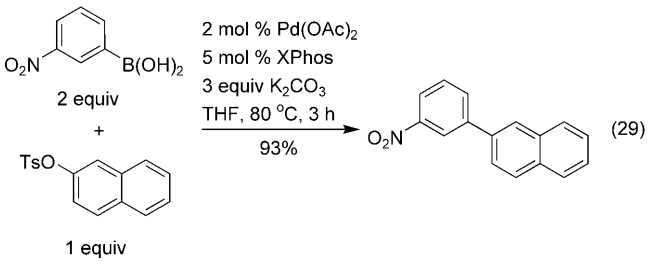
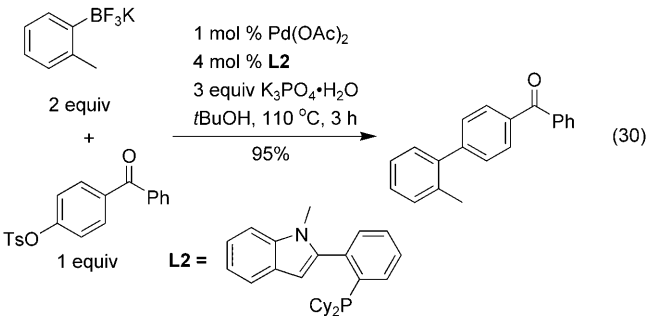


(29)

trifluoroborate under the same conditions employed for the analogous boronic acids [Eq. (30)].[65] Most unusually, aryl mesylates have been developed as electrophilic partners for organotrifluoroborates in the presence of the same indolylphosphine ligand [Eq. (31)].[66] Mesylates are much less reactive than the corresponding tosylates in cross-coupling reactions, but the Kwong research group determined in a limited study that organotrifluoroborates are as effective as boronic acids and pinacol boronates.



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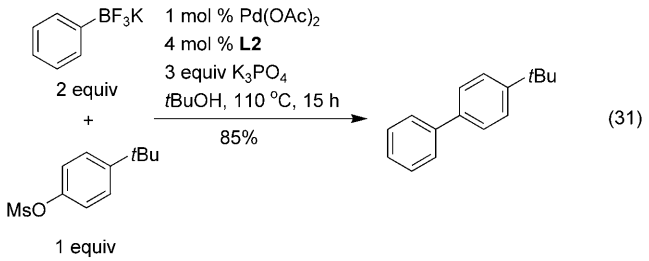
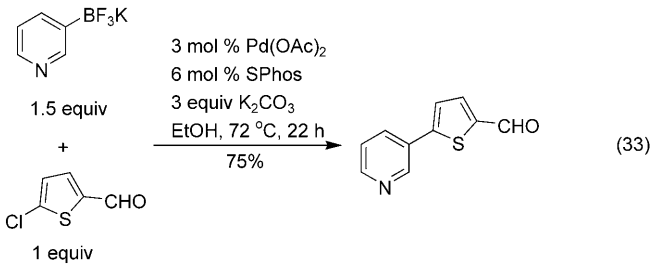


(31)

One of the biggest challenges in the cross-coupling arena has been to find widely effective and broadly applicable procedures for heteroaryl organoboron species. As pointed out above, some heteroaryl boronic acids are highly susceptible to proto-deboronation, with cleavage of the carbon–boron bond occurring over 10^6 times faster in these species than in electronically neutral phenylboronic acid.[32b,33] Thus, not only do many of these heteroaryl boronic acids decompose upon storage, but under the conditions of the cross-coupling, boronic acids undergo a competitive proto-deboronation. Consequently, most protocols for the cross-coupling of aryl boronic acids and MIDA complexes advocate the use of a 10–50% or more excess of the boron reagent to assure that enough nucleophile is available for coupling with the electrophilic aryl halide partners.[32b,67]

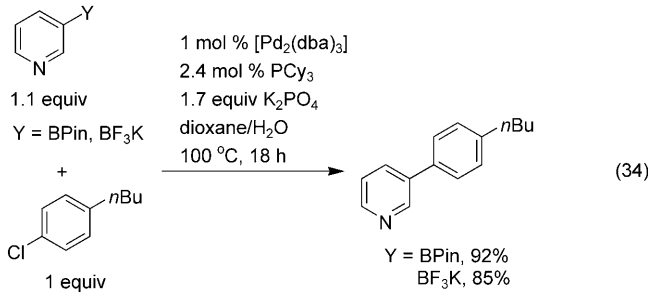
Some early studies had already alluded to the value of utilizing highly optimized, monocoordinated palladium complexes as catalysts in conjunction with heteroaryl trifluoroborates as a means of resolving the daunting challenge of bringing about efficient coupling. For example, Barder and Buchwald used SPhos in conjunction with pyridin-2-yltrifluoroborate as a means to cross-couple aryl and heteroaryl chlorides effectively [Eqs. (32) and (33)].[58] In a related study,

(32)



(33)

Fu and co-workers determined that organotrifluoroborates performed nearly as well as pinacol boronates when PCy_3 was used as a ligand [Eq. (34)].[68] Organ and co-workers examined a single case of heteroaryl trifluoroborate cross-coupling with an aryl bromide in the presence of their PEPPSI catalyst system [Eq. (35)].[60]



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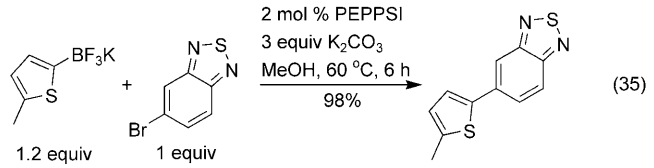
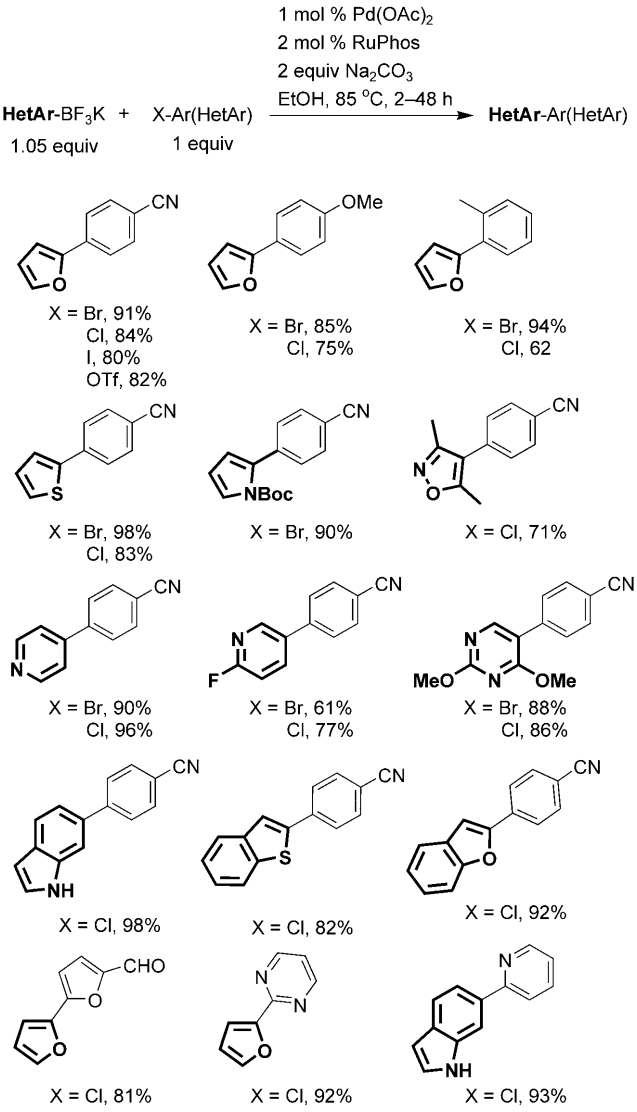


(35)

The most comprehensive study along these lines, however, demonstrated that the combination of potassium heteroaryl trifluoroborates with monocoordinated palladium complexes as catalysts was ideal for accomplishing the targeted cross-coupling reactions (Scheme 14).[69] In this study, furan-2-yltrifluoroborate was chosen as the test substrate because previous studies[70] had revealed that the corresponding

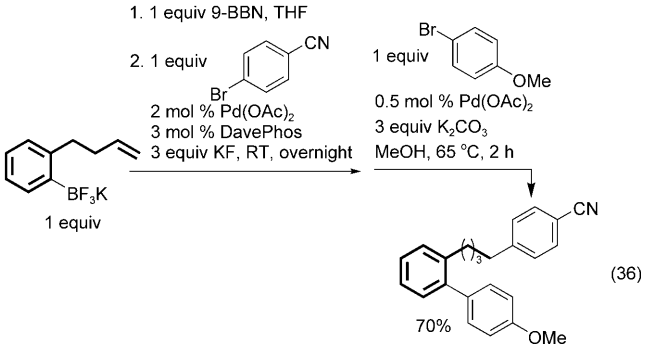


Scheme 14. Cross-coupling of heteroaryl trifluoroborates.

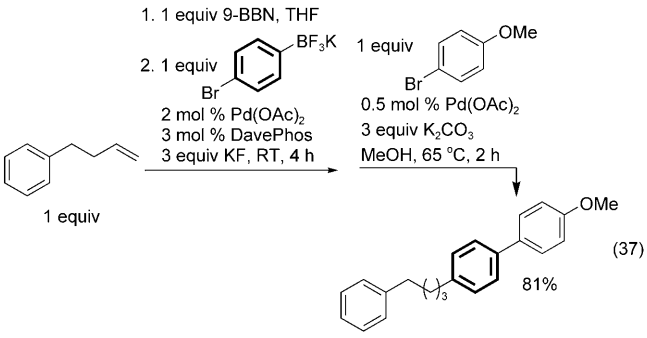
boronic acid provided none of the cross-coupled product in a system optimized for other heteroaryl boronic acids. The heteroaryl trifluoroborate study not only revealed that these reagents exhibit an indefinite shelf life, but a general set of reaction conditions was developed that allowed high yields in the cross-coupling of 23 structurally diverse heteroaryl trifluoroborates. Furthermore, the conditions were milder than those used in most previously reported transformations, used reasonably low catalyst loadings, and employed an environmentally friendly solvent.

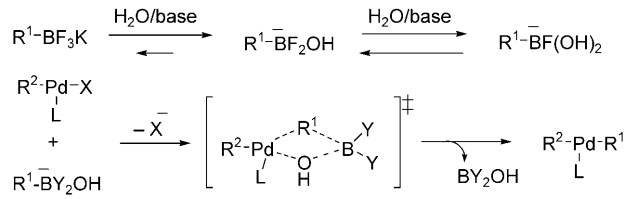
Advantage can be taken of the trifluoroborate as a protected boronic acid to perform chemoselective cross-coupling reactions in the presence of other organoboron species.[50] This concept can take several forms. In the first, an unsaturated aryl trifluoroborate can be hydroborated with 9-

BBN, and the resulting organoborane can be cross-coupled under anhydrous conditions, leaving the organotrifluoroborate unit intact. The addition of a second electrophile under protic conditions triggers the coupling of the trifluoroborate unit, thus resulting in a one-pot, three-component cross-coupling sequence [Eq. (36)]. In this case, DavePhos serves as an effective ligand for coupling with both alkyl-9-BBN and aryl trifluoroborates.



In a second version of this concept, an alkyl-9-BBN reagent can be treated with an aryl halide bearing a trifluoroborato group. The alkyl-9-BBN is selectively coupled, again leaving the aryl trifluoroborate untouched. The addition of a second electrophile and a protic solvent initiates the coupling of the organotrifluoroborate, thereby completing the one-pot, three-component coupling [Eq. (37)]. Both of these reaction sequences rely on the fact that alkyl-9-BBN reagents can be coupled under anhydrous conditions, but as mentioned previously, organotrifluoroborates require protic conditions to facilitate transmetalation (Scheme 15).[52]



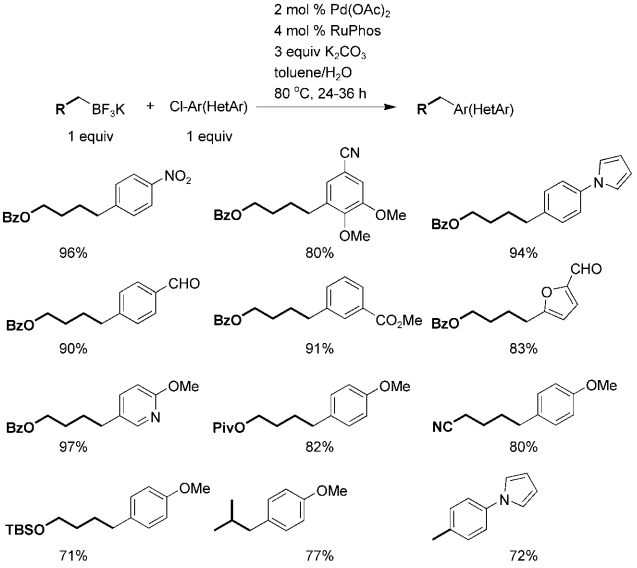


Scheme 15. Hydrolysis of organotrifluoroborates to facilitate transmetalation. X = halogen; Y = OH, F; L = phosphine.

4.2. Cross-Coupling with Alkyl Trifluoroborates

The cross-coupling of alkyl groups is a second arena in which the combination of organotrifluoroborates and monoligating, electron-rich ligands excels. Both a slower transmetalation and the potential intervention of β-hydride elimination from the intermediate alkyl palladium species conspire to provide a severe challenge to successful processes. In fact, because of competitive proto-deboronations that normally required the use of a large excess of boronic acids, only a few examples of the successful coupling of alkyl boronic acids to aryl chlorides had been reported[71] prior to the initial report of the same process involving alkyl trifluoroborates.[72] The relative resistance of alkyl trifluoroborates to proto-deboronation makes them particularly favorable in situations where transmetalation is slow. This aspect, combined with the beneficial features of the monoligating ligands that enhance the rate of reductive elimination relative to β-hydride elimination, makes the combination of these two particularly powerful.

In a contribution that highlighted the value of high-throughput experimentation on a microscale for the optimization of synthetic methods,[72] general conditions were found for the coupling of primary alkyl trifluoroborates with a variety of aryl and heteroaryl chlorides. Among the 72 ligands screened, RuPhos was determined to give the optimal results (Scheme 16). Not only were a variety of electrophiles



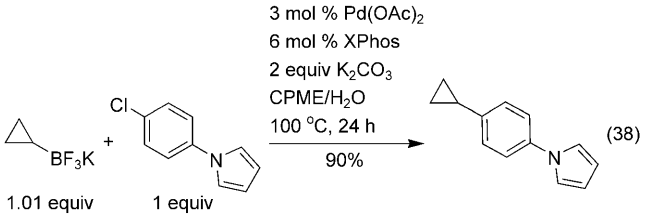
Scheme 16. Cross-coupling of alkyl trifluoroborates.

tolerated, but a range of alkyl trifluoroborates possessing a diverse array of functional groups was also accommodated in the process.

It is perhaps useful to point out that even when β-hydride elimination does not compete with cross-coupling, the combination of organotrifluoroborates with monocoordinated palladium complexes as catalysts has advantages. Thus, methyltrifluoroborate reacts with an electron-rich aryl chloride in the presence of a relatively low loading of

$Pd(OAc)_2$/RuPhos (Scheme 16). When the $[PdCl_2(dppf)]\cdot CH_2Cl_2$ system is used, 9 mol% of the catalyst system is required to react with more reactive, electron-poor aryl bromides.[73]

Cyclopropylboronic acid is inherently unstable and undergoes proto-deboronation upon storage for any period of time.[32b] The corresponding cyclopropyltrifluoroborate, on the other hand, is indefinitely resistant to this phenomenon. Although aryl bromides and iodides had previously been coupled with cyclopropyltrifluoroborates in the presence of $[Pd(PPh_3)_4]$,[74] the use of aryl chlorides had not been reported, and $[Pd(PPh_3)_4]$ or $[PdCl_2(dppf)]$ in conjunction with aryl chlorides proved ineffective.[75] A screening of seven ligands demonstrated that XPhos was an excellent choice for accomplishing the cross-coupling of cyclopropyltrifluoroborate with a variety of aryl chlorides [Eqs. (38) and (39)].



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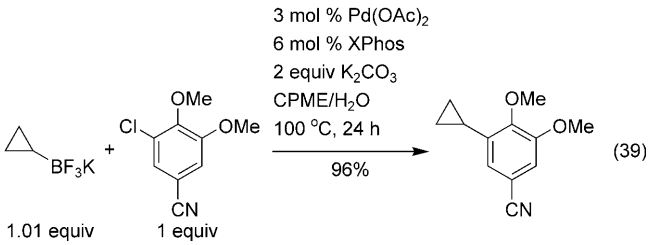
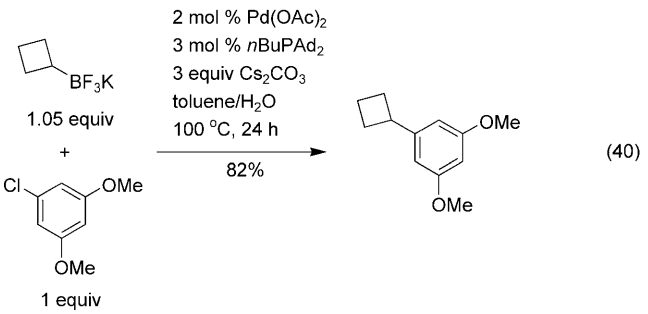


(39)

A similar screening with heteroaryl chlorides revealed that CataXCium A was a superior ligand in these systems, with the XPhos ligand and several others failing to provide optimal yields of the desired product. A number of different heteroaryl chloride substructures were used in the reaction, and generally gave excellent yields (Scheme 17).[75]

Under the same reaction conditions, cyclobutyltrifluoroborate also undergoes effective cross-coupling, and represents the first Suzuki–Miyaura reaction of a cyclobutylboron reagent [Eq. (40)].[75]



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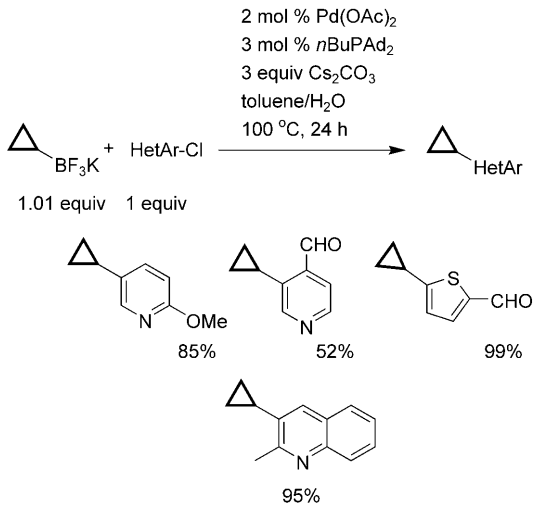
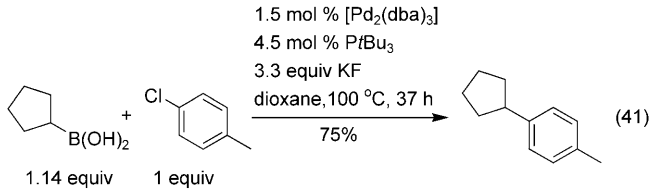


Scheme 17. Cross-coupling of cyclopropyltrifluoroborates.

One of the most demanding cross-coupling reactions to date has been the coupling of secondary (and potentially enantioenriched) alkyl boron compounds with aryl halides. Prior to 2008, there had been only two examples of this type of coupling, both using boronic acids in conjunction with sterically encumbered, electron-rich ligands [Eqs. (41) and (42)].[76] Unfortunately, no further development to generalize the process was reported.



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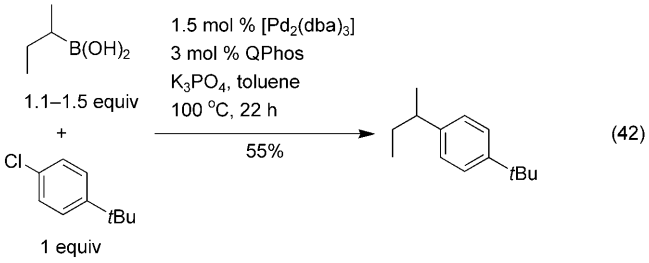
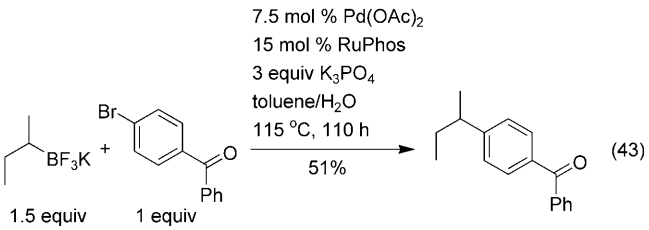


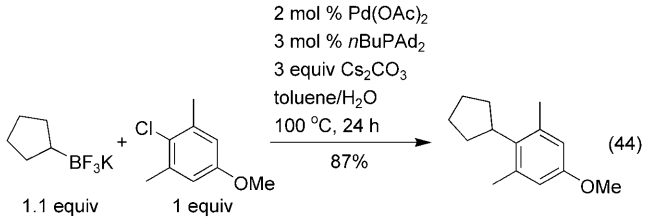
(42)

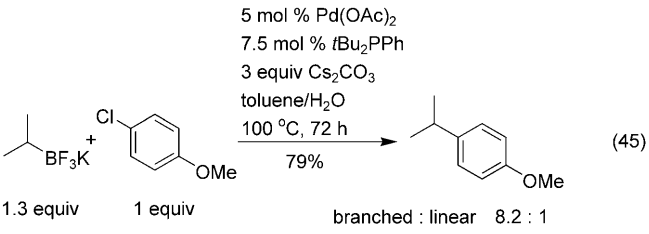
In 2008 van den Hoogenband et al. reported a RuPhos-mediated cross-coupling of secondary alkyl trifluoroborates with aryl bromides.[77] In general, the yields were modest and a 50% excess of the alkyl trifluoroborate along with a high catalyst loading was utilized to achieve optimal results [Eq. (43)].

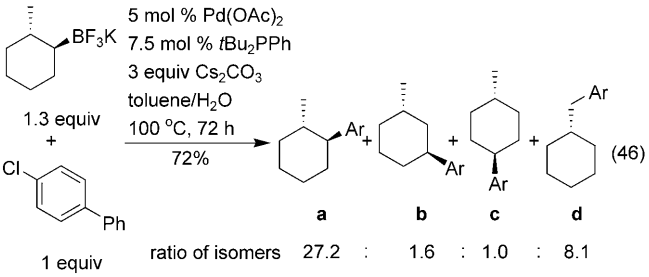
Independently, high-throughput screening on a microscale was used to provide a more satisfactory, but still not general, solution. By screening 3 different solvent systems and 12 ligands previously shown to be effective in related coupling reactions, effective conditions were determined for the fusion



of several different secondary alkyl trifluoroborates with a range of aryl and heteroaryl chlorides [Eqs. (44)–(46)].[78] Some isomerization as a result of β-hydride elimination and reinsertion was still observed in sterically hindered systems,

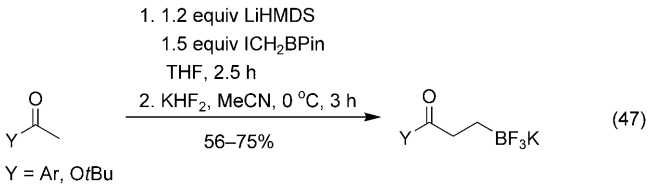


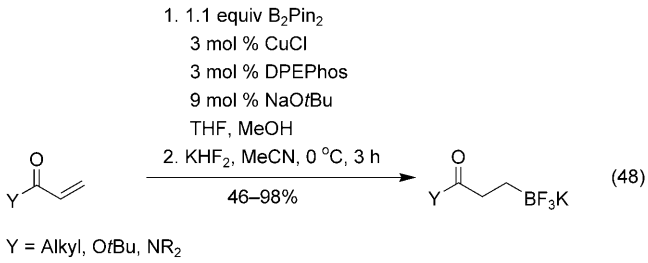




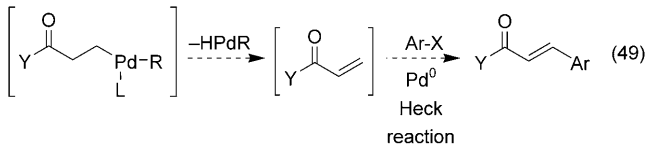
which will require further ligand design and optimization. Nevertheless, these studies do provide a pathway to the ultimate goal of developing a set of enantiomerically pure substrates for cross-coupling which react to give the secondary organometallic reagent with complete stereochemical fidelity.

Within the realm of alkyl trifluoroborates there exist several specialized sets of reagents that bring new dimensions and possibilities to cross-coupling processes. One such set of reagents are 3-oxo-substituted alkyl trifluoroborates. These can be prepared in two fundamentally different ways: either by alkylation of enolates with halomethylpinacol boronates [Eq. (47)][79] or by conjugate addition of bis(pinacolborane) to unsaturated carbonyl substrates [Eq. (48)].[80] In this manner, β-trifluoroboratoketones, -esters, and -amides can all be readily prepared. Although more-reactive β-metallo ketones react irreversibly to form cyclopropanoxides[81] or must be kept dry under an inert atmosphere, the organotrifluoroborates are nonhygroscopic free-flowing powders or crystalline solids, indefinitely stable to the atmosphere.

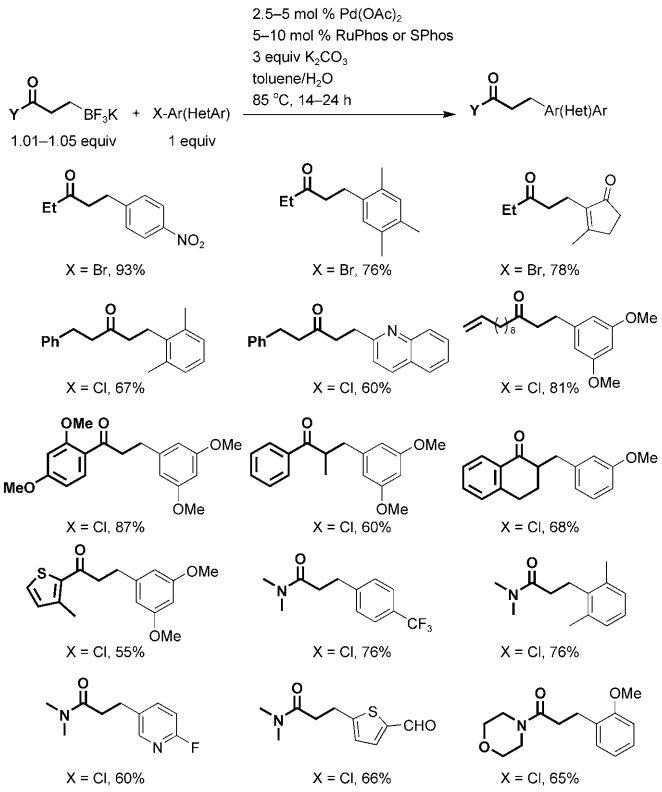




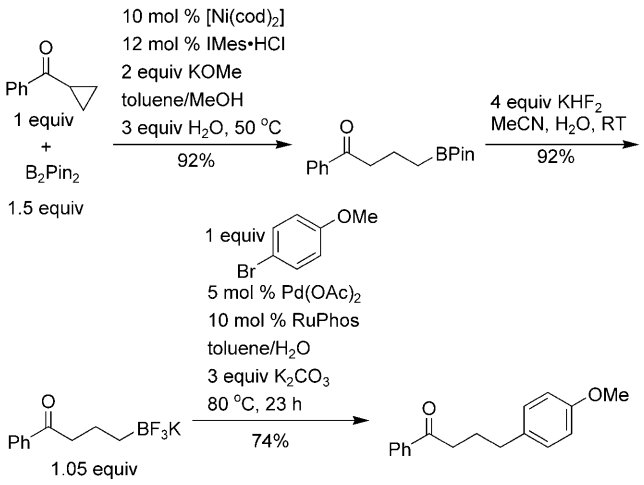
Although the cross-coupling of 3-oxoalkylzinc compounds derived from esters was extensively investigated prior to the emergence of the corresponding organotrifluoroborates,[82] the analogous process for the ketone and amide derivatives was apparently unknown. Indeed, there were reports that suggested that β-hydride elimination from the diorganopalladium species derived from the ketones was exceedingly rapid and led to α,β-unsaturated carbonyl compounds and subsequent Heck-type reactions [Eq. (49)].[82,83] By contrast, the 3-oxoalkyl trifluoroborates, in combination with monocoordinated palladium complexes as catalysts, were found to undergo cross-coupling reactions with a variety of aryl and heteroaryl halides and triflates under a standard set of conditions, with little or no evidence of the products derived from β-hydride elimination (Scheme 18).[84] The success of this process can be attributed to the enhanced rate of reductive elimination brought about by the sterically hindered, electron-rich biaryl phosphine ligands.



Synthetic approaches to the homologous 4-oxoalkyl trifluoroborates and their subsequent cross-coupling have also been examined.[85] A nickel-catalyzed borylative ring opening of cyclopropyl ketones leads to the creation of 4-oxoalkyl boronates (Scheme 19). Treatment of the generated compounds with KHF_2 produces the alkyl trifluoroborates in



Scheme 18. Cross-coupling of 3-oxoalkyltrifluoroborates.

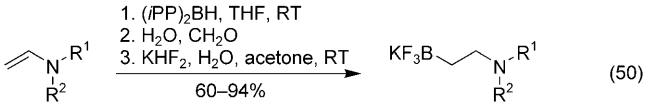


Scheme 19. Preparation and cross-coupling of 4-oxoalkyltrifluoroborates.

near quantitative yield. The organotrifluoroborates can be cross-coupled under conditions similar to those developed for the coupling of 3-oxoalkylboronates, with the coupled product formed in good yield.

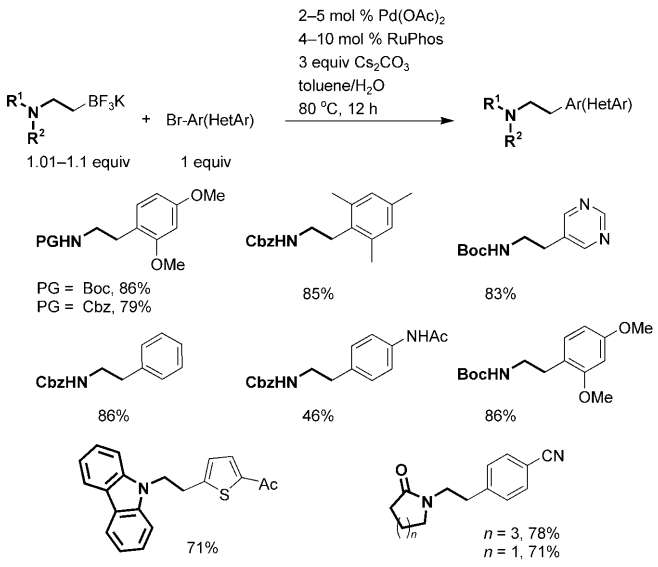
Efficient aminoethylation reactions with organotrifluoroborates have also been developed. A precedent for this process was reported by the Overman research group,[86] who utilized reagents generated in situ by the hydroboration of enecarbamates with 9-BBN. This procedure is highly efficient, with several distinct advantages (for example, the reactions can be performed at room temperature, and, once optimized, the one-pot version is most efficient). However, for late-stage steps in natural product synthesis, where the generation and cross-coupling of an air-sensitive material on a small scale may be difficult, the use of a solid that can be prepared in advance and accurately weighed can be of advantage. Such shelf-storable material is also of benefit in diversity-oriented synthesis, where the substrate can be prepared and measured out in suitable quantities for cross-coupling with a variety of electrophilic partners.

β-(Aminoethyl)trifluoroborates are readily prepared from enamines, enamides, and enecarbamates by hydroboration with bis(isopropylprenyl)borane [(*i*PP)$_2$BH] followed by treatment with formalin and then aqueous KHF_2 [Eq. (50)].[87]



(50)

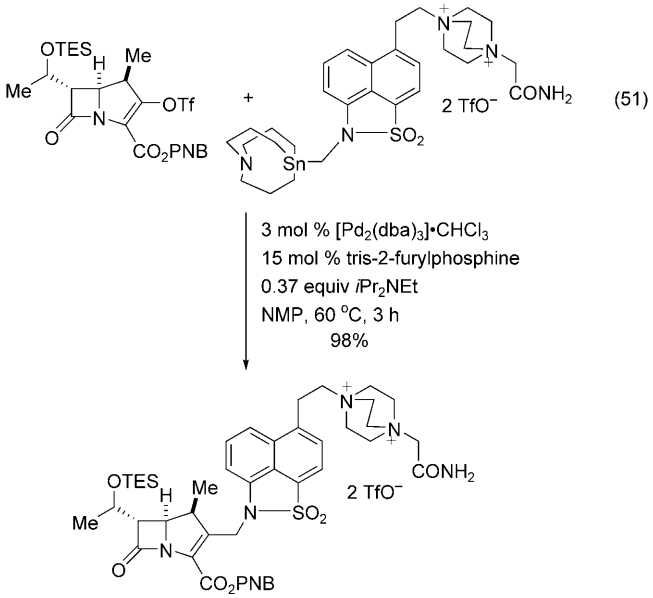
In many cases [$PdCl_2$(dppf)]·CH_2Cl_2 was an adequate catalyst for the cross-coupling of these species, but when difficulties were encountered Pd(OAc)$_2$/RuPhos proved much more effective. Thus, the transformation of organotrifluoroborates derived from enamides benefited greatly by using the RuPhos system, as did enecarbamate-derived alkyl trifluoroborates in their coupling with electron-rich aryl bromides and heteroaromatic bromides (Scheme 20).



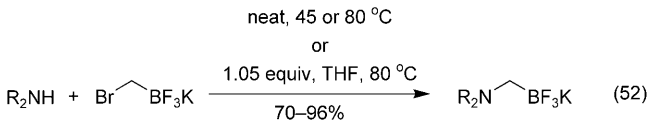
Scheme 20. Cross-coupling of β-aminoethyltrifluoroborates.

Of perhaps greater interest and importance are aminomethylation reactions. The aminomethyl group is a widely used functional group in pharmacologically active materials, usually prepared by the reductive amination of aldehydes or alkylation of amines derived from aromatic nitriles. The cross-coupling of aminomethylorganometallic reagents provides a

complementary route to this important substructure. Prior to the development of the aminomethyltrifluoroborate route to this structural motif, a single example of this coupling had been reported. This involved the coupling of a highly complicated aminomethylstannane with an enol triflate, which resulted in the creation of an elaborate β-lactam derivative [Eq. (51)].[88]

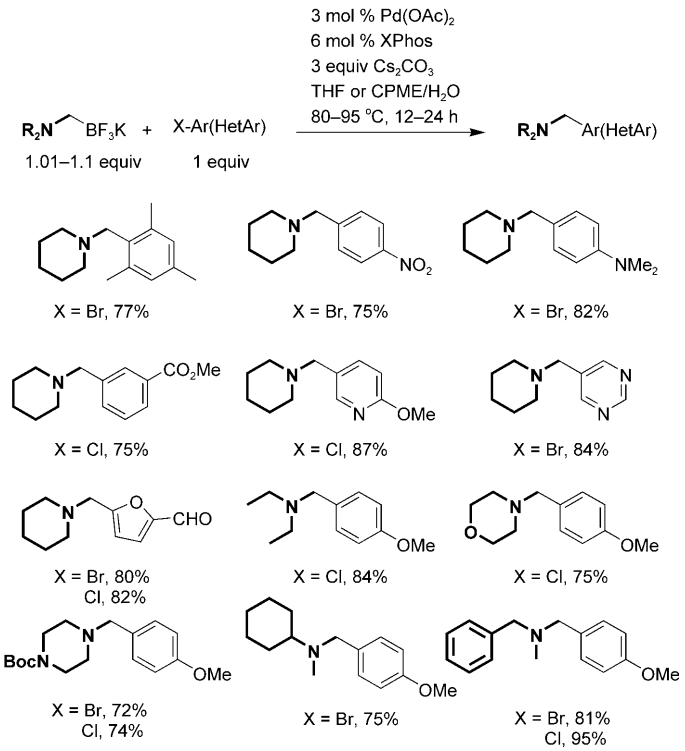


The aminomethyltrifluoroborates required for the cross-coupling are readily prepared by a simple S_N2 reaction of various amines with commercially available bromomethyltrifluoroborate [Eq. (52)].[46a,89] Depending on the nature of the



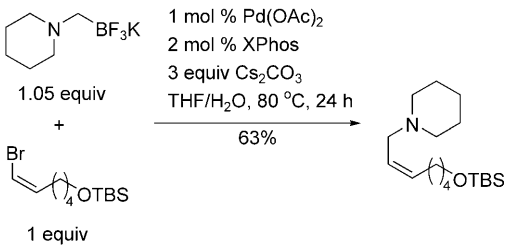
requisite amine, one of two different protocols can be utilized: 1) If the amine is a liquid and less expensive than THF, the substitution reaction can be prepared in neat amine. 2) If the amine is a solid and/or is more expensive than THF, a slight excess of the amine can be used in THF to accomplish the desired conversion.

After an extensive screening effort, XPhos was determined to be the most efficacious ligand to promote the cross-coupling.[46a,90] Aryl iodides, bromides, chlorides, and triflates all coupled well under a standard set of conditions, and diverse heteroaryl chlorides were also suitable substrates in the process (Scheme 21). As might be anticipated, aryl bromides react selectively in the presence of aryl chlorides, while aryl tosylates did not react. The use of a diverse range of aminomethyltrifluoroborates lends credibility to the process as a suitable complement to reductive amination.



Scheme 21. Cross-coupling of aminomethyltrifluoroborates.

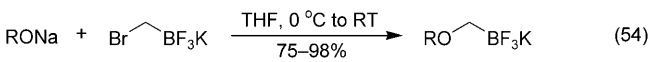
Further studies revealed that alkenyl bromides could be cross-coupled under similar conditions, thus permitting a novel route to allylamines [Eq. (53)].[90]



The analogous alkoxymethylation reaction results in the synthesis of benzyl ethers.[91] Although such structures are readily prepared by the formation of a C–O bond between alkoxides and benzylic halides, the complementary C–C bond-forming alkoxymethylation reaction has a clear advantage in many cases because of substrate availability. Thus, although a substantial number of aryl and heteroaryl halides used as electrophiles in the alkoxymethylation are commercially available, relatively few benzylic or pseudobenzylic halides required for a Williamson ether synthesis are available.

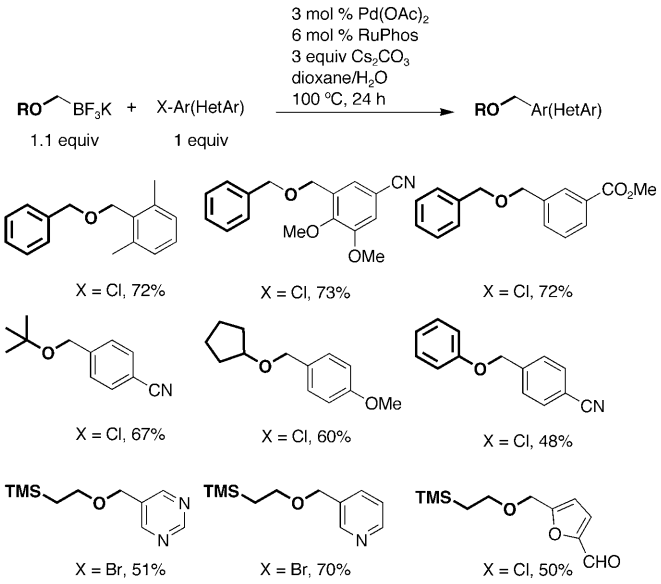
A limited number of alkoxymethylations of organostannanes were known prior to the development of the alkoxymethyltrifluoroborates,[92] but the perceived toxicity of tin compounds and lack of atom economy, combined with difficulties associated with removing tin-containing by-prod-

ucts, makes them relatively unattractive starting materials for synthesis. In analogy with the aminomethyltrifluoroborates mentioned above, the alkoxymethyltrifluoroborates are also prepared from bromomethyltrifluoroborate, but using alkoxide nucleophiles [Eq. (54)].[46a]



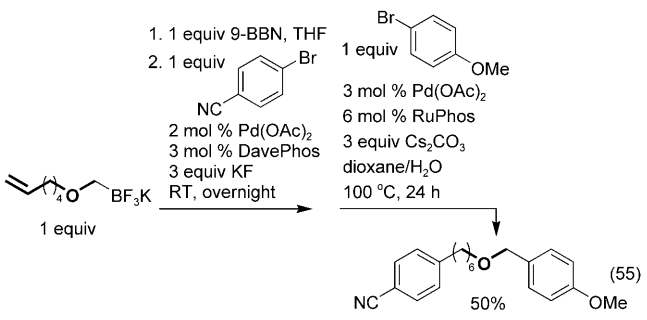
(54)

Screening efforts in this case again led to a universal set of conditions that allowed the coupling of a variety of alkoxymethyltrifluoroborates with aryl and heteroaryl chlorides and bromides (Scheme 22).[91]



Scheme 22. Cross-coupling of alkoxymethyltrifluoroborates.

Sequential, multicomponent coupling processes were developed in which the participating alkyl trifluoroborate serves as a protected form of a boronic acid.[50a] Thus, unsaturated alkyltrifluoroborates can be hydroborated with 9-BBN to generate a species in situ with two different boron groups. The alkyl borane can be cross-coupled with one aryl halide under anhydrous conditions, and the addition of a protic solvent induces reaction of the alkyl trifluoroborate with a second added electrophile [Eqs. (55) and (56)].



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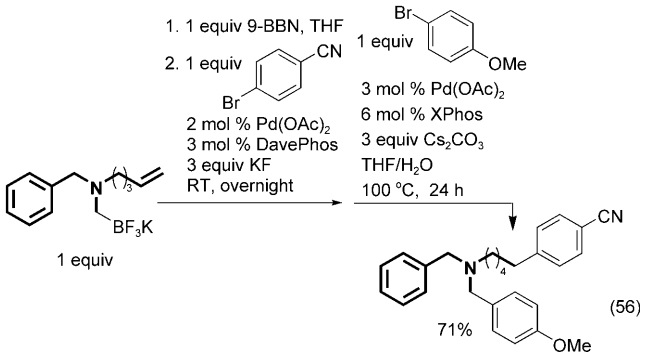
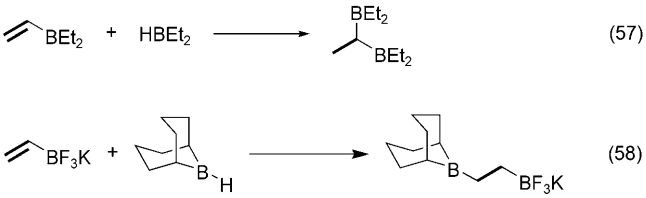


(56)

In conjunction with vinyltrifluoroborate, this process becomes a means to link two different electrophiles through an ethyl 1,2-dianion equivalent via a chemically differentiated 1,2-diboraethane species.[50b] The hydroboration of vinyl dialkylboranes provides 1,1-dibora species [Eq. (57)]. However, the trifluoroborato group reverses the regioselectivity of this process to afford 1,2-dibora compounds [Eq. (58)]. As in previous examples, the 9-BBN moiety can be induced to cross-couple under anhydrous conditions, whereas the trifluoroborate couples only upon the addition of protic solvent. In this manner, aryl, heteroaryl, and alkenyl groups can be conveniently and efficiently linked in any order by an ethane unit [Eqs. (59)–(63)].



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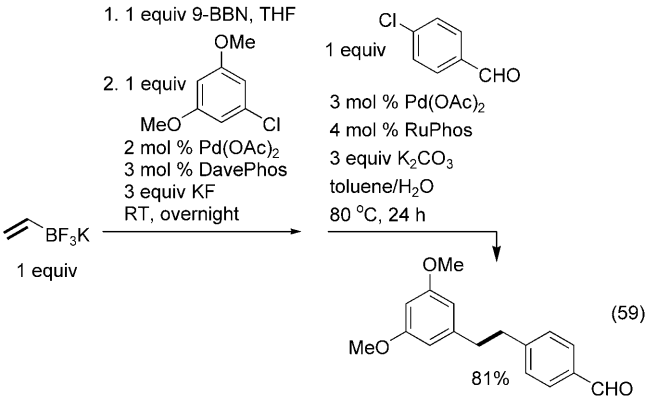
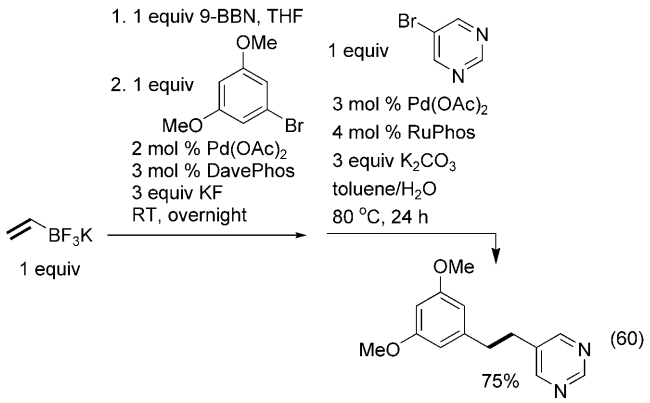
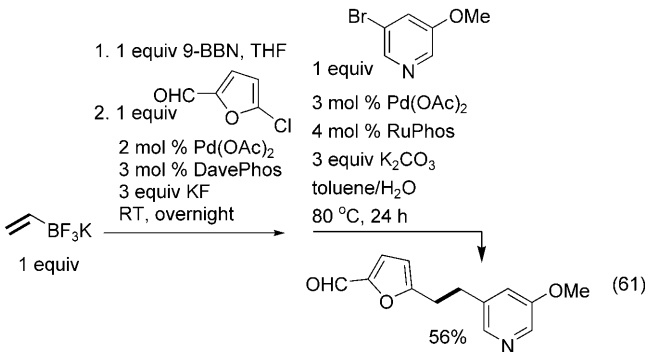


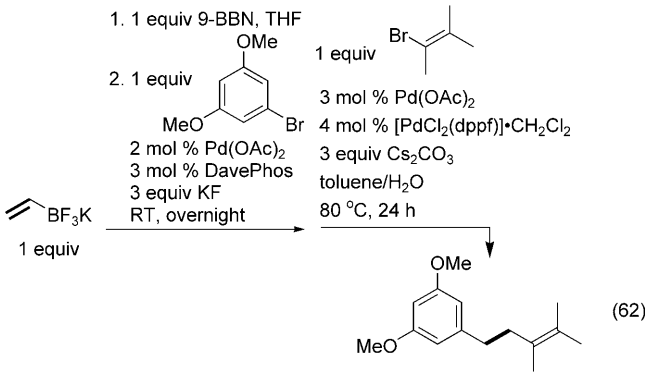
(59)

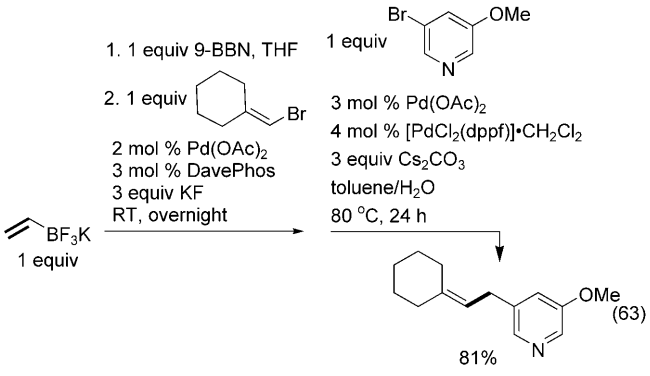
5. Conclusions

Many significant advances have taken place in cross-coupling reactions since its inception. Their ready availability, low toxicity, and tolerance of functional groups have resulted









in the cross-coupling with boronic acids emerging as the clear favorite among the various protocols developed. The original Suzuki–Miyaura procedure, developed in response to inadequacies in the formation of $C(sp^2)$–$C(sp^2)$ bonds, has been expanded to include transformations that were simply not possible at the time. Although many aspects of the reaction underwent incremental improvements over the first 20 years, the introduction of monocoordinated palladium complexes as catalysts and a detailed understanding of their efficacy represented a quantum leap in terms of the capabilities of the reaction, thereby allowing more favorable reaction conditions and even novel transformations that might previously have been deemed impossible.

Significantly, these transformations were so successful that little development of the boron reagents themselves was undertaken. This has now changed. With the advent of the organotrifluoroborates, a more robust class of reagents has been introduced which, in combination with modern ligands, has reinvigorated research into the Suzuki–Miyaura reaction. The organotrifluoroborates not only represent reagents with significantly enhanced physical properties, but also unique chemical properties as well. The organotrifluoroborates undergo coupling under conditions that, in many cases, are more favorable than those of the parent boronic acids. Their stability allows unique reagents and therefore bond connections to be produced. Finally, organotrifluoroborates can be considered as protected forms of boronic acids, thus permitting significant elaboration of organic substructures bearing the trifluoroborate without affecting the C–B bond. This protection function also allows selective reaction at one boron species in the presence of another. The organotrifluoroborates thus give new life to an already very versatile key reaction, further enhancing its critical role in synthetic organic chemistry.

Abbreviations

Ad	adamantyl
9-BBN	9-borabicyclo[3.3.1]nonane
Boc	*tert*-butoxycarbonyl
bn	benzyl
Cbz	benzyloxycarbonyl
CPME	cyclopentyl methyl ether
cod	1,5-cyclooctadiene
Cy	cyclohexyl
dba	dibenzylideneacetone
DPEPhos	bis(2-diphenylphosphinophenyl)ether
dppf	1,1′-bis(diphenylphosphino)ferrocene
dtbpy	4,4′-di-*tert*-butyl-2,2′-bipyridine
HMDS	1,1,1,3,3,3-hexamethyldisilazane
NMP	*N*-methyl-2-pyrrolidinone
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
QPhos	1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TMS	trimethylsilyl
TPPTS	tris(3-sulfonatophenyl)phosphine, trisodium salt
Ts	toluene-4-sulfonyl

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